MCRs to APIs

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Summary

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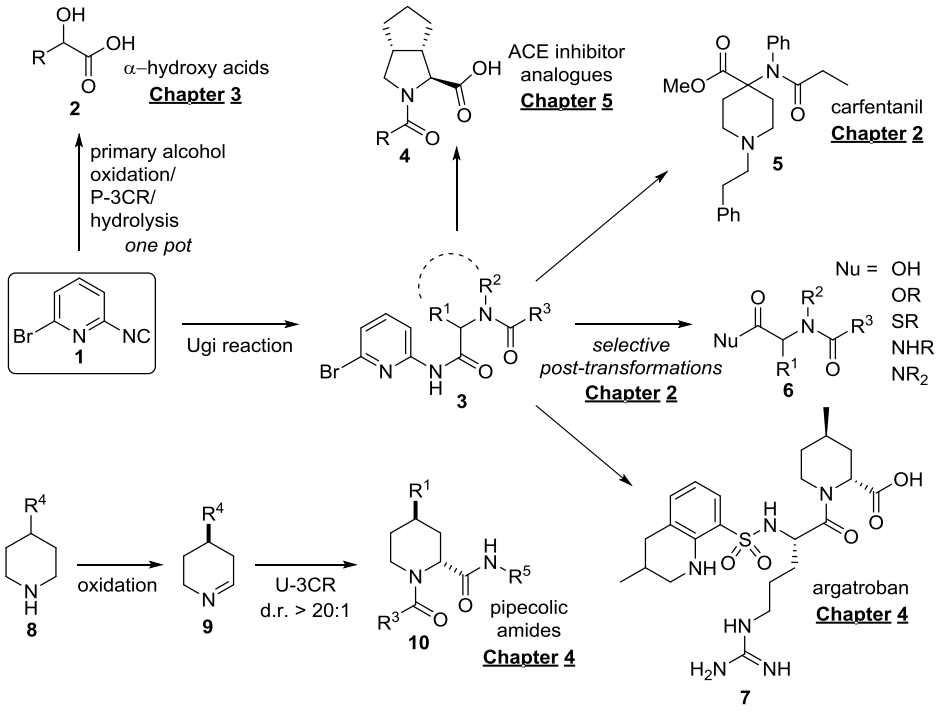
Tailoring Multicomponent Reactions for the Production of Pharmaceuticals

The pharmaceutical industry invests a lot of time and resources in the discovery of new and improved drugs. A large number of the current set of drugs and probably also a large number of the future drugs have a very complex molecular structure. Nowadays, for a well-trained organic chemist it is not the question if the active target drug can be synthesized, but rather how efficiently it can be done. The traditional lengthy, linear synthetic approaches are very expensive and go hand in hand with the generation of vast amounts of chemical waste. Therefore, there is a demand for clean and efficient methods to synthesize these challenging compounds with high atom economy and other green metrics. Multicomponent reactions (MCRs) are excellent tools for these goals. In MCRs, three or more reagents are selectively combined to form a structurally complex scaffold, ideally with all atoms of the starting materials incorporated.

One of the most important reaction inputs of MCRs are isocyanides. These versatile reagents have both a nucleophilic and electrophilic character. As a result of their unique reactivity they participate in many MCRs, including the Ugi and Passerini reactions. The utility of isocyanide chemistry in the synthesis of natural products and pharmaceuticals is rapidly increasing, as demonstrated by the selected examples in **Chapter 1**.

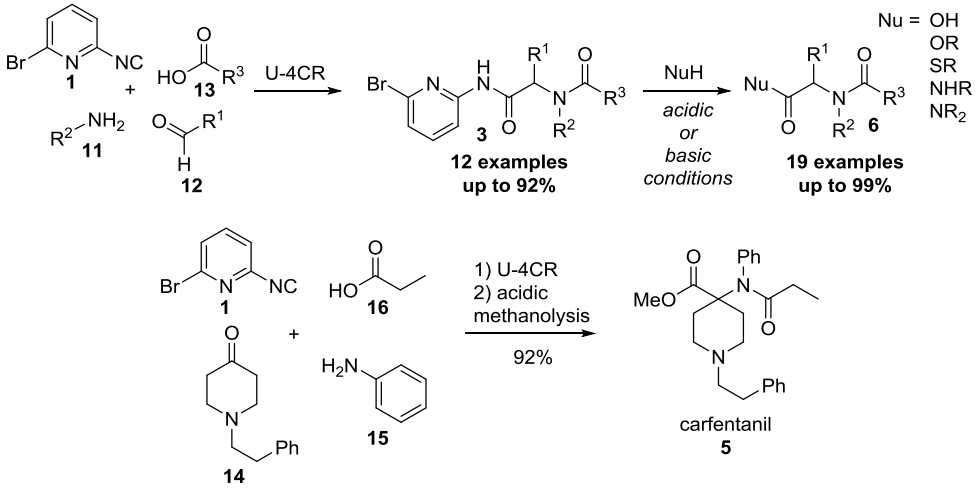
Although isocyanide-based multicomponent reactions (IMCRs) offer many advantages compared to linear synthesis, they also suffer from some severe limitations: (*i*) The products of IMCRs generally have the same molecular skeleton, (*ii*) the commercial availability of many isocyanides is limited and (*iii*) the IMCR products generally contain a new stereocenter, which is difficult to control. The key objective of this thesis is to address the above mentioned limitations of IMCRs by the development of a novel convertible isocyanide and with the use of diastereoselective IMCRs (Scheme 1). These methods offer significant advantages in the synthesis of pharmaceutically relevant compounds.

The first two limitations (*i* and *ii*) of IMCRs can be resolved by the use of a convertible isocyanide. In the past decades many convertible isocyanides have been developed for a broad range of chemically different post transformations (**Chapter 1**). However, the current set of convertible isocyanides generally suffers from some severe disadvantages, including the stability/handling of the isocyanide, its multistep and/or tedious synthesis or the difficult and/or harsh post-transformation conditions.



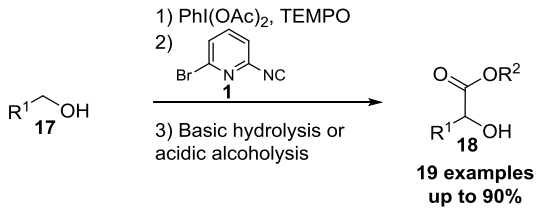
Scheme 1. Overview of various targets of chemistry with 2-bromo-6-isocyanopyridine.

We envisioned the use of 2-isocyanopyridines as novel class of convertible isocyanides (**Chapter 2**). The electron-withdrawing properties of the pyridine ring make the resulting secondary amide sufficiently electrophilic for a nucleophile to attack the activated carbonyl under basic reaction conditions. On the other hand, the basic pyridine nitrogen can be protonated under acidic conditions, which also enhances the electrophilicity of the secondary amide to make it more susceptible to nucleophile attack. Comparison of several different isocyanopyridines indicated that 2-bromo-6-isocyanopyridine (**1**) is the best candidate for both the IMCR and post-transformation. The isocyanide **1** performed well in many Ugi four-component reactions (U-4CRs) and the resulting secondary amides of the Ugi products were readily converted to the corresponding carboxylic acids (Scheme 2). Furthermore, the secondary amides of the Ugi products (**3**) were transformed into other functional groups, such as (thio)esters and amides, under both basic and acidic conditions. Finally, we demonstrated the utility of the isocyanide in the efficient synthesis of the extremely potent narcotic carfentanil (**5**) in only two reaction steps.



Scheme 2. Applicability of 2-bromo-6-isocyanopyridine in the U-4CR and in the synthesis of carfentanil.

The efficiency and convertibility of the isocyanide prompted us to investigate other IMCRs such as the Passerini reaction (**Chapter 3**). Oxidation of a primary alcohol (**17**) with $PhI(OAc)_2$ and a catalytic amount of TEMPO results in the corresponding aldehyde together with two equivalents of acetic acid (Scheme 3). Addition of isocyanide **1** to the reaction mixture provides the Passerini product. Finally, hydrolysis of both the activated secondary amide and the ester group with aqueous NaOH furnishes the α-hydroxy acids (**18**, R^2 = H). The one-pot oxidation/Passerini/hydrolysis sequence tolerates a broad range of functional groups on the primary alcohol input. Furthermore, a minor modification to the reaction conditions extends the range of accessible products to α-hydroxy esters (**18**, R^2 = alkyl).

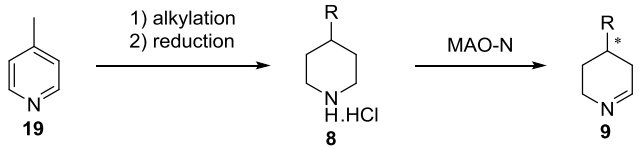


Scheme 3. One-pot synthesis of α-hydroxy acids and esters.

Our next goal was to gain control in the stereoselectivity of IMCRs. Since there is no asymmetric catalyst available for the U-4CR, we were interested in the use of optically pure reaction inputs for the U-4CR that can induce diastereoselectivity. Previously, we described the use of an engineered variant of monoamine oxidase (MAO-N D5) for the oxidation of 3,4-disubstituted *meso*-pyrrolidines to the corresponding imines in high

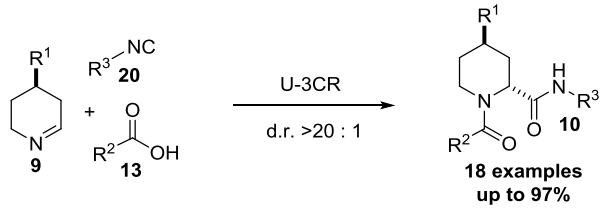
optical purity (**Chapter 4**). These 1-pyrrolidines are excellent substrates for an U-3CR to obtain the corresponding prolyl peptides in good to excellent diastereomeric ratios.

We envisioned that we could extend the above mentioned methodology to the oxidation of prochiral 4-substituted piperidines (**8**) with MAO-N (**Chapter 4**). The 4-substituted piperidines were synthesized by an efficient two-step procedure involving alkylation of 4-picoline (**19**) and subsequent catalytic hydrogenation of the pyridine ring involving catalytic PtO_2 (Scheme 4). The parent MAO-N D5 variant showed limited activity for the piperidine substrates. Fortunately, the activity was greatly enhanced by several rounds of directed evolution with MAO-N D5 and D9 as parent enzymes.



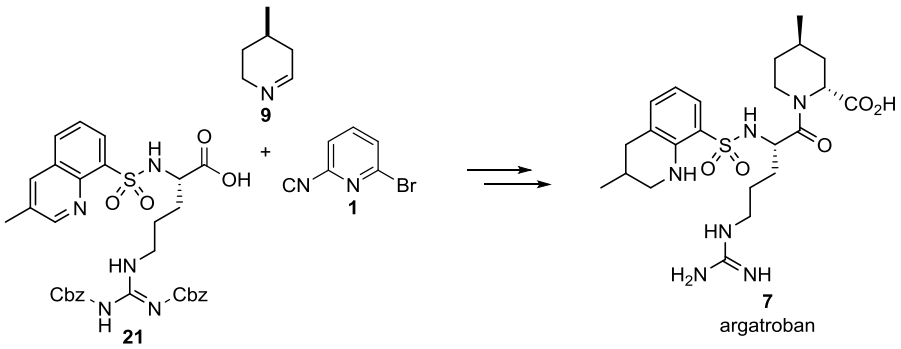
Scheme 4. Biocatalytic synthesis of enantiomerically enriched Δ^1-piperideines.

Alternatively, the 4-substituted piperidines (**8**) can be chemically oxidized to racemic Δ^1-piperideines **9** by *N*-chlorination with NCS followed by elimination with ethanolic KOH. These Δ^1-piperideines proved very suitable inputs for the U-3CR in combination with chemically diverse isocyanides (**20**) and carboxylic acids (**13**) leading to a wide variety of biologically interesting pipecolic amides (**10**). Interestingly, the reaction proceeded with excellent diastereoselectivity. The substituent on the piperidine input fully controlled the newly formed stereocenter of the pipecolic amides.



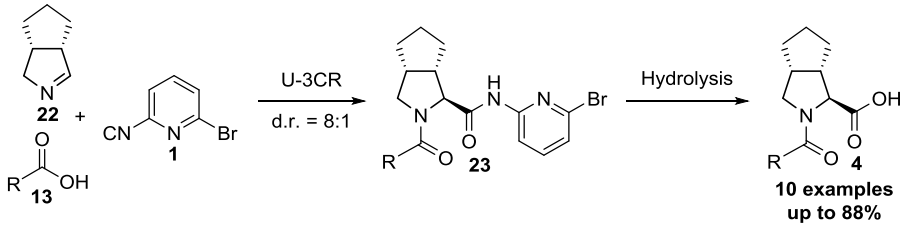
Scheme 5. Diastereoselective synthesis of pipecolic amides.

As a demonstration of the potential of the U-3CR, we used our methodology in combination with our recently developed convertible isocyanide 2-bromo-6-isocyanopyridine (**1**) as a key step in the synthesis of the anticoagulant argatroban (**7**, Scheme 6). The synthesis is convergent and requires only protection of the guanidine group of the arginine residue.



Scheme 6. Key step of the synthesis of argatroban.

We then decided to investigate the use of 1-pyrrolidine **22** in combination with 2-bromo-6-isocyanopyridine (**1**) to obtain *N*-functionalized proline derivatives **4** after hydrolysis of the activated amide of Ugi products **23** (**Chapter 5**). The resulting carboxylic acids **4** strongly resemble the class of ACE inhibitors. The synthesis of structural analogues is crucial for the discovery of more potent derivatives. To demonstrate the utility of this methodology, we composed a small library with the use of chemically diverse carboxylic acids (Scheme 7).



Scheme 7. Synthesis of ACE inhibitor analogues.

In conclusion, the results described in this thesis indicate that IMCRs are very valuable tools for the synthesis of complex, optically pure compounds. The general shortcomings of IMCRs are tackled by the development of 2-bromo-6-isocyanopyridine as novel convertible isocyanide and with the use of highly diastereoselective IMCRs with enantiomerically enriched imine inputs derived from a biocatalytic oxidation with MAO-N. The value of this new methodology is demonstrated by the synthesis of known drugs and libraries of other pharmaceutically relevant compounds.